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(54) Title: PHARMACEUTICAL FORMULATIONS

(57) Abstract: The application discloses novel pharmaceutical formulations adapted for delaying the release of a pharmaceutically active agent. A delayed-release drug formulation encapsulates the active ingredient, which may be applied to microparticles or in tableted form, in a release-delaying coat comprising polymeric materials of predetermined swelling/permeability characteristics. In particular, acrylate and/or acrylic acid polymer blends modified with ionic groups may be used. One preferred embodiment uses a polymer of pH dependent permeability as a more permeable element of the coat. The delayed-release formulations are deployed in a single dosage form together with instant release or sustained release formulations, so that a unit dosage form, preferably an oral dosage form, can effectively administer two doses to a patient at different times.

Pharmaceutical Formulations

Field of the Invention

The present invention relates to methods of pharmaceutical formulation and administration, and in particular, orally administrable formulations capable of providing a desired pharmacokinetic profile for an active agent.

Background to the Invention

Many pharmaceutically active agents are metabolised by mammalian systems. Any dosing regime must take into account the pharmacokinetic properties of the active ingredient and its interaction with the metabolic system of the subject in order to obtain the required pharmacokinetic profile and bioavailability of the drug. It may be desirable to achieve a slow sustained release rate of a pharmaceutically active agent. This is ideal where a single administration or dose of an active agent is required to act over a long time period, especially where metabolism or degradation of the drug will not significantly reduce its bioavailability.

However, metabolism or degradation can seriously impair bioavailability of many drugs. In such cases, the method of administration must be tailored in order to overcome the problems associated with drug metabolism. The metabolism of some active agents may be saturable. Where this is the case, a pulse of active ingredient sufficient to saturate the relevant metabolic or degradative pathway can enable a therapeutically acceptable quantity of active agent to be delivered to the target tissue or organ.

It is desirable to produce a single dose form of administration capable of releasing a pulse of active agent, as provided by an immediate release formulation, after a specified lag period. Combination of one or more such dosage forms with immediate release and/or sustained release formulations may enable a single dose formulation to provide multiple, temporally distinct pulses of active agent to a patient. Such a combination would reduce the need for multiple dose administration regimes, and could therefore have significant benefits, for example, in improving patient compliance.

Thus there is a need for novel modes of administration of pharmaceutically active agents capable of delivering tailored release of active agents.

Summary of the Invention

We have developed a method of formulating active ingredients to provide novel orally administrable pharmaceutical formulations or dosage forms giving delayed or sustained release of the active agent.

One object of the present invention is to provide sustained release formulations, capable of releasing active ingredient over a required time period. A further object of the present invention is to provide delayed release formulations capable of delivering a pulse of active agent, similar to that obtained with an immediate release formulation, after a suitable delay period.

A further object of the invention is to provide a dosage form capable of releasing active agent at two different release rates. In a preferred embodiment the dosage form

is capable of releasing active agent in two distinct peaks, separated by an appropriate time period. Typically the peaks will be separated by at least two hours, possibly at least five hours, possibly at least 8 hours.

Accordingly, the present invention provides a particulate oral dosage form comprising a pharmaceutically active agent, the dosage form also comprising a release modifying layer, the release modifying layer comprising a polymer having solubility properties predetermined to affect the rate of release of the active agent under enteric physiological conditions.

The particulate dosage form may be manufactured as a multiparticulate formulation. This may be a granulate, or alternatively a pellet or "non-pareil" type formulation, in which the active agent is applied to an inert support. The particulate dosage form may also be manufactured in a "minitablet" type formulation, in which the active agent is compressed into a minitablet with appropriate excipients.

Thus, in one embodiment, the pharmaceutically active agent is applied to an inert, particulate, pharmaceutically acceptable support. In a preferred embodiment the inert, particulate, pharmaceutically acceptable support comprises carbohydrate beads, such as non-pareil seeds (often referred to as neutral pellets, or sugar spheres).

The active ingredient may be sprayed onto the inert, particulate, pharmaceutically acceptable support from

solution, preferably an aqueous solution. Alternatively, the active ingredient may be coated onto the inert, particulate, pharmaceutically acceptable support from suspension, for example, by means of a fluidised bed coating system such as a Wurster system. The active agent may be applied to the inert, particulate, pharmaceutically acceptable support alone or in combination with further pharmaceutically acceptable excipients.

In a further embodiment, the particulate dosage form may be manufactured as a "minitablet" formulation of the pharmaceutically active agent. Minitablets may be formed by the direct compression of active agent with fillers such as microcrystalline cellulose, lactose, dicalcium phosphate, lubricants such as magnesium stearate or stearic acid, disintegrants such as sodium starch glycolate and glidants such as colloidal silicon dioxide. Minitablets may also be formed by wet granulation of the drug with suitable excipients in a fluidised bed.

These particulate dosage forms will typically initially constitute "immediate release" type formulations, whose release properties may be altered by application of suitable coatings, as will be described below. Typically the active agent will constitute 1 to 20%, preferably 3 to 10%, of the total weight of the immediate release particulate dosage form prior to the application of any coating.

The particulate dosage form may also comprise a protective sealant or barrier coat, applied to the particulate dosage form. Preferably, this protective

sealant or barrier layer is soluble and does not substantially modify the release of the active drug under physiological conditions, but protects it during processing. In one embodiment, the protective coat is composed mainly of hydroxypropyl methylcellulose. Other agents can be added to improve the processability of the sealant layer. The protective coat can be applied from solution, such as an aqueous solution, or suspension using a fluidised bed coater (for example, a Wurster system), or in a pan coating system.

Minitablet formulations may include excipients which affect the rate of dissolution of the minitablet, and thus the rate of release of the active agent. Such minitablet formulations may be regarded as "sustained release" type minitablets before any modifying coatings are applied. Their release properties may be further modified by application of release modifying coatings. Thus, minitablets providing sustained release of the active agent may be formed by the direct compression or wet granulation of the drug with excipients, as described above, plus the inclusion of rate controlling excipients such as hydroxypropylcellulose, polyethylene glycolate and ethylcellulose, typically in a concentration of 20-80%.

The release profile of the active agent can be modified according to the present invention by applying a modifying coating of material having predetermined dissolution properties to the particulate dosage form. Such a modifying coating may be used to provide a sustained release profile or a delayed release profile for the active agent, and typically comprise soluble

polymers (with solubility being pH independent or pH dependent) that can modify the release of the drug.

For example, a "sustained release" type formulation may release between 2.5% and 25% of the active agent in 0.5 hours, between 25% and 70% of the active agent in 1 hour, between 65% and 95% of the active agent in 2 hours, and at least 90% of the active agent in 4 hours, as determined in standard USP method II dissolution assay, in phosphate buffer at pH 6.8 (as described later). Thus a typical sustained release formulation may provide approximately 10% release of the active agent in 0.5 hours, approximately 50% release of the active agent in 1 hour, approximately 75% release of the active agent in 2 hours, and approximately 95% release of the active agent in 4 hours. The release profile required will vary depending on the active agent employed and the pharmacokinetic profile desired.

In preferred embodiments the modifying coating may comprise soluble or permeable acrylate polymers, e.g. ammonio methacrylate polymers or co-polymers, or methacrylic acid polymers or co-polymers. The polymers can be used alone or in combination with each other. Additionally or alternatively such modifying materials may be blended with active agent as a matrix ingredient.

The coatings can also include other agents to improve the processability of the coating. Examples of such agents include talc, silicon dioxide and glyceryl monostearate. The quantity of such anti-caking agents used for preparing coatings for the dosage form is e.g. from about 2% to about 100% by weight, preferably 30 to 60%, based

on the total dry weight of the polymer.

The coatings can also include a material that improves the characteristics of the polymer material. Such materials are generally referred to as "plasticisers" and include, for example, dibutyl sebacate (DBS), diethyl phthalate, citric acid esters, or triethyl citrate (TEC), stearates, polyethylene glycols and ethylene glycol. Dibutyl sebacate or triethyl citrate are the preferred plasticisers. The amount of plasticiser to be used in the coating is preferably from about 10% to 50%, most preferably about 20%, based on the weight of the dry polymer.

The coating solutions can also include an anti-foaming agent. An example of such an agent is simethicone emulsion. The amount of anti-foaming agent to be used in the coating is preferably from less than 0.5% of the final coating solution.

The amount of coating to be used in preparing the dosage form will be determined by the desired delivery properties, including the amount of drug to be delivered, the time delay desired, and the size of the particles. The coating polymers will typically be coated from 5 to 20% weight gain on the instant release particles, preferably 6-10% polymer weight gain. The polymer layer can be coated by any known method, including spray application. Spraying can be carried out using a fluidised bed coater (preferably using a Wurster system), or in a pan coating system.

The coated particles can be dried and/or cured after

application of the polymer layers. "Curing" means that the particles are held at a controlled temperature for a time sufficient to provide stable release rates. Curing can be performed for example in an oven or in a fluid bed drier. Curing can be carried out at temperature within 25° and 50°C, preferably 35° to 45°C.

The particulate dosage form may, alternatively or additionally, be coated with a modifying layer able to modify the release of the active agent, to form delayed release particles.

The process and the materials used to prepare a delayed release coating can be similar to those used to provide sustained release coatings, as described above. More particularly, however, we envisage a delayed release or sustained release coating comprising a blend of a relatively insoluble or impermeable polymeric material with a more soluble or permeable material, the choice of polymers and the proportions in the blend controlling the release rate. A particularly preferred embodiment uses for the relatively permeable polymer a polymer whose permeability or solubility is pH dependent; in particular being more soluble or permeable in alkaline conditions than in acidic conditions. This enables passage of the coating through the stomach relatively undisrupted, for release of the active agent further along the gut. For sustained release the pH dependence of polymer solubility or permeability may not be needed. A pH dependent system may be used to provide a delay in initial drug release. It may also be used to provide protection against acid degradation of acid labile drugs in the gut and/or maximise the concentration of drug available to

absorption sites in the intestine.

Film forming polymers which are swellable or soluble under appropriate conditions and suitable for oral formulation, are available commercially and known to the skilled person, e.g. Eudragit polymethacrylate coating systems from Röhm. Poly(meth)acrylates with varying proportions of ionic groups in the acrylate-forming moiety, e.g. quaternary ammonium salt groups, can be used to provide correspondingly varying film permeabilities. Eudragit L may be used to provide drug release in the duodenum/jejunum, and Eudragit S for release in the ileum.

One particular novel procedure proposed herein is to form a release-delaying coating from a blend of film-forming, swellable acrylate polymers of any suitable kinds as described herein, one of which is in aqueous dispersion (latex) and the other of which is in non-aqueous dispersion (latex), creating a characteristic and useful difference in film permeability behaviours of the two polymers in the layer.

The amount of coating to be used may be determined by the desired delivery properties, including the amount of drug to be delivered, the time delay desired, and the size of the particles. The modifying layer will typically provide 15 to 80% weight gain on the uncoated or sustained release particles, preferably 15 to 40% polymer weight gain on a first layer and possibly 5 to 30% polymer weight gain on a subsequent layer. The first and subsequent layers may have identical or different compositions.

Increasing the amount of coating increases the distance the drug has to travel by diffusion through the swelled or permeabilised polymer film to be released into the surrounding medium, and therefore reduces the rate of drug release by diffusion. Decreasing the proportion of permeable component will give less opportunity for the drug to be directly solubilised by the dissolution medium and therefore may provide a longer lag time before drug release begins.

Typically, the particulate dosage forms will be encapsulated into individual doses. Administration is preferably in a "prophylactically effective amount" or a "therapeutically effective amount", as the case may be (although prophylaxis may be considered therapy), this being sufficient to show benefit to the individual. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of the condition to be treated. Prescription of treatment, e.g. decisions on dosage etc, is within the responsibility of general practitioners and other medical doctors, and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners. Examples of the techniques and protocols mentioned above can be found in Remington's Pharmaceutical Sciences, 16th edition, Osol, A. (ed), 1980.

It is envisaged that one or more varieties of the particulate dosage forms may be encapsulated together. The quantity of particles filled into any individual capsule will vary depending on the active agent to be

administered, the specific activity of the active agent in the particular particulate dosage form, and the pharmacokinetic profile required. Any combination of the above described components may be encapsulated to obtain a desired release profile, and they may be combined in various ratios or strengths. For example, uncoated neutral pellet ("non-pareil") type multiparticulates providing an initial release, and coated neutral pellet ("non-pareil") type multiparticulates providing a delayed release, may be encapsulated together e.g. in a hard gelatine capsule, preferably using standard dual filling encapsulation equipment. Alternatively sustained or delayed release minitablets could be encapsulated with instant release non-pareil seeds. Depending on the formulations, any one of the possible component types may contribute to initial, sustained or delayed release elements of the overall pharmacokinetic profile provided.

Specific embodiments of the present invention will now be described in more detail by way of example, with reference to the accompanying Figures, in which:

Figure 1 shows dissolution profiles for sustained release multiparticulate formulations.

Figure 2 shows dissolution profiles for delayed release multiparticulate formulations.

Figure 3 shows dissolution profiles for sustained release minitablet formulations without a modifying coat.

Figure 4 shows dissolution profiles for sustained release minitablet formulations coated with Eudragit RS/RL

Figure 5 shows dissolution profiles for delayed release minitablet formulations.

Figure 6 shows dissolution profiles for co-encapsulated

sustained release minitablets and delayed release multiparticulate formulations.

Experimental

For formulations comprising pH dependent polymer, dissolution profiles were established by immersion of test formulation for two hours in 0.01M HCl, followed by immersion in pH 6.8 phosphate buffer. For formulations comprising only pH independent polymer, the immersion in acid was omitted, and test formulations were immersed in pH 6.8 phosphate buffer for the duration of the assay. Aliquots of the dissolution buffers were removed at intervals and analysed for released rivastigmine by HPLC.

Buffers

0.01M HCl was prepared by diluting 8.5ml of concentrated HCl 1 litre with de-ionised water to give a solution of 0.1M HCl. This was then diluted to 0.01M HCl with deionised water, and then degassed by sparging with helium at 1.2 litres/min for 20 minutes.

1 litre of phosphate buffer (pH6.8 ± 0.05) was prepared by adding 250ml of 0.2M potassium phosphate solution (27.22g of monobasic potassium phosphate (KH_2PO_4) per litre distilled water) to 112ml of 0.2M sodium hydroxide solution and diluting to 1000ml with distilled water. Phosphate buffer was degassed as above.

Dissolution

Test formulation corresponding to 12.5mg of rivastigmine base was placed into a clean dry dissolution basket assembly (USP Apparatus I, with 40 mesh baskets). The

basket was attached to the apparatus shaft, lowered into a dissolution vessel containing 500ml 0.01M HCl or phosphate buffer at 37.0 ± 0.5°C, and rotated at 100rpm.

For pH dependent formulations, after two hours dissolution time, the 0.01M HCl was neutralised by addition of approximately 50ml 0.1N NaOH to the vessel, with mixing. The basket was then transferred to a second dissolution apparatus containing 500ml phosphate buffer (pH 6.8).

At each time point, a 4ml aliquot of dissolution buffer was removed and filtered through a Millipore Millex-HV Hydrophilic PVDF 0.45mm filter into a suitable vial for analysis by HPLC, discarding approximately the first 2ml of filtrate to waste. The volume removed at each sampling time point was replaced with 4ml pre-heated media.

Rivastigmine content of the samples was analysed by HPLC as described below.

HPLC analysis

Column: PUROSPHER ® (RP-18) 5mm, 12.5 cm x 4.0mm i.d. LiChroCart [(Cartridge), Merck, Germany] or equivalent.

Temperature: 40 ± 1° C

Mobile phase: 1 litre of mobile phase was prepared by adding 670ml of HPLC grade methanol to 330ml of aqueous buffer (3.85g - 3.95g of ammonium carbamate (anhydrous form of

carbonate) dissolved in 1 litre of deionised water). The mobile phase was filtered and degassed for 10 minutes with helium. The pH was adjusted to 9.2 as necessary with conc. ammonia.

Flow Rate: 1.7 ml/min.

Injection Volume: 50µl.

UV Detection: 214nm

Retention of active ingredient: $t_{RENA\ 713} \geq 1.5$min

HPLC was calibrated with duplicate standards, each prepared by accurately weighing 20mg of rivastigmine tartrate reference standard (equivalent to 12.5mg Rivastigmine base) into a 500ml volumetric flask. This was dissolved and diluted to 500ml with medium, mixed well and an aliquot filtered through a Millipore Millex-HV Hydrophilic PVDF 0.45mm filter into a suitable vial for injection, discarding approximately the first 2ml of filtrate to waste.

The calibration was accepted if:

1. The difference between the weight corrected peak response for the two rivastigmine standard solutions was not greater than 2.0%.

2. The coefficient of variation for five injections of

a single rivastigmine reference solution was not greater than 2.0%.

Calculations

The formulae given below (at 1 and 2) can be used to calculate the release of active agent from sample formulations with pH independent and pH dependent polymer coatings.

1. **Formulation comprising only pH independent polymers**

For a formulation comprising only pH independent polymer, with samples taken at 0.5 hours, 1 hour, 2 hours, 4 hours and 6 hours:

A. Uncorrected amount of rivastigmine (free base) released (in mg)

$$M_H = \frac{A_{sample} \times Wt_{std} \times DF \times P \times F}{A_{std}}$$

B. Correction factor (for each time point)

$$Q_H = \frac{M_H \times V_S}{V_{diss}}$$

C. The corrected hourly release of rivastigmine

$$T_{0.5} \quad R_{0.5} = M_{0.5}$$
$$T_1 \quad R_1 = M_1 + Q_{0.5}$$
$$T_2 \quad R_2 = M_2 + Q_1 + Q_{0.5}$$
$$T_4 \quad R_4 = M_4 + Q_2 + Q_1 + Q_{0.5}$$

$$T_6 \quad R_6 = M_6 + M_4 + Q_2 + Q_1 + Q_{0.5}$$

D. The corrected amount of rivastigmine (free base) released

$$\% \text{ Released} = \frac{R_H \times 100}{\text{Potency}}$$

Where:-

H = sampling time intervals

M_H = mg of rivastigmine (uncorrected) released per hour

$A_{samp.}$ = response of sample

A_{std} = response of standard

DF = dilution factor = $\frac{500}{500} = 1.0$

W_{std} = weight of standard (mg)

V_{diss} = volume of dissolution medium (500ml)

Q_H = correction factor (mg of rivastigmine free base)

V_s = volume of sample withdrawn at each interval (4ml)

R_H = corrected hourly release (mg)

% R = corrected % released for each interval

Potency = mg/sample

P = Correction factor for purity of standard (if less than 100%)

F = 0.625 to convert rivastigmine tartrate to free base

2. Formulation comprising pH dependent polymers

For a formulation comprising pH dependent polymer, with one sample taken from acid at 2 hours, and subsequent samples taken from phosphate buffer at two-hourly intervals:

A. _ Uncorrected amount of rivastigmine (free base) M released (in mg):

$$M_H = \frac{A_{sample} \times Wt_{std} \times DF \times P \times F}{A_{std}}$$

B. Correction factor Q (for each time point):

$$Q_H = \frac{M_H \times V_S}{V_{diss}}$$

C. The corrected amount of rivastigmine R released at each time point T is given by:

T_2 R_2 = M_2
T_4 R_4 = $M_4 + Q_2$
T_6 R_6 = $M_6 + M_4 + Q_2$
T_8 R_8 = $M_8 + Q_6 + M_4 + Q_2$
T_{10} R_{10} = $M_{10} + Q_8 + Q_6 + M_4 + Q_2$
T_{12} R_{12} = $M_{12} + M_{10} + Q_8 + Q_6 + M_4 + Q_2$

D. The corrected amount of rivastigmine (free base) released:

$$\% \text{ Released} = \frac{R_H \times 100}{\text{Potency}}$$

Where:-

H = sampling time intervals

M_H = mg of rivastigmine (uncorrected) released per hour

$A_{samp.}$ = response of sample

A_{std} = response of standard

DF = dilution factor = $\frac{500}{500} = 1.0$

W_{tstd} = weight of standard (mg)

V_{diss} = volume of dissolution medium (500ml)

Q_H = correction factor (mg of rivastigmine free base)

V_s = volume of sample withdrawn at each interval (4ml)

R_H = corrected release for each time interval (mg)

% R = corrected % released for each interval

Potency = mg/sample

P = Correction factor for purity of standard (if less than 100%)

F = 0.625 to convert rivastigmine tartrate to free base

Example 1: Preparation of instant release (IR) Rivastigmine multiparticulates.

A solution of hydroxypropyl methylcellulose was prepared by adding 100.0g of hydroxypropyl methylcellulose into 1.900kg of purified water and continuing mixing for 45 minutes.

A suspension of Rivastigmine tartrate was prepared as follows. To 1106.6g of hydroxypropyl methylcellulose solution were added 265.7g of Rivastigmine tartrate. The

mixture was stirred for 15 minutes to dissolve the drug. 27.7g of silicon dioxide were added to the solution and the mixture was stirred for 15 minutes.

A protective solution was prepared as follows. To 682.9g of hydroxypropyl methylcellulose solution were added 17.1g of silicon dioxide and the mixture was stirred for 15 minutes.

The Rivastigmine suspension was sprayed first onto 2.500kg of 0.85-1.00mm non-pareil seeds in a fluid bed apparatus (GPCG-3, Glatt) equipped with a Wurster 7" chamber. After the equivalent of 5% Rivastigmine free base weight gain was layered onto the non-pareil seeds, 1.75% weight gain of the protective solution was applied onto the cores. The spray rate for drug layering was 3.2-4.8g/min*kg, the inlet temperature was 47-50°C and the cores were maintained at 34-38°C. The drug loaded instant release multiparticulates were cooled in the Glatt GPCG-3 for 20 minutes. The multiparticulates were screened to remove oversized beads and fine material.

Example 2: Preparation of sustained release (SR) Eudragit RS:RL (98:2) coated Rivastigmine multiparticulates.

Rivastigmine instant release multiparticulates (prepared according to Example 1) were coated with Eudragit RS: Eudragit RL (98:2) aqueous dispersion.

A Eudragit RS: Eudragit RL (98:2) aqueous dispersion was prepared as follows: 0.5g of Simethicone emulsion USP,

120.0g of DBS and 360g of talc USP were added with mixing to 2.515kg of purified water. The mixture was stirred for 15 minutes in a high shear mixer at 6000 rpm. The suspension was added to 1.960kg of Eudragit RS 30D and 40.0g of Eudragit RL 30D (ammonio methacrylate co-polymers in the form of aqueous dispersions from Röhm Pharma, Germany) and stirred for 20 minutes.

A polymer weight gain of 12% was coated onto the Rivastigmine coated multiparticulates and in process samples were taken at 6, 8 and 10% polymer coating. The coated multiparticulates were cured in an oven at 40°C for 40 hours, then screened to remove oversized multiparticulates and fine material.

Table 1 shows dissolution rates for sustained release multiparticulates. These profiles are illustrated in Figure 1.

Table 1

	Eudragit RS: RL (98:2) DBS			
	% released			
Time (hours)	6%	8%	10%	12%
0.5	55.9	23.0	3.4	N/T
1	80.1	61.4	32.2	
2	96.4	91.0	69.1	
4	97.7	94.6	90.5	
6	99.2	97.7	96.6	

Example 3: Preparation of delayed release (DR) Eudragit RS:RL (90:10) coated Rivastigmine multiparticulates.

A Eudragit RS: Eudragit RL (90:10) aqueous dispersion was prepared as follows: 0.5g of simethicone emulsion USP, 120.0g of triethyl citrate and 360g of talc USP were added with mixing to 2.515kg of purified water. The mixture was stirred for 15 minutes is a high sharer mixer at 6000 rpm. The suspension was added to 1.800kg of Eudragit RS 30D and 200g of Eudragit RL 30D (ammonio methacrylate co-polymers in the form of aqueous dispersions from Röhm Pharma, Germany) and stirred for 20 minutes.

The resulting combined dispersion was sprayed onto instant release multiparticulates prepared according to Example 1, using a fluid bed apparatus as used in Example 1. Spray rate was 3.5-15g/min/kg, the inlet temperature was 38-42°C and the cores temperature was 25-30°C. A polymer coating of 40% polymer weight gain was coated onto the instant release multiparticulates and an in process sample was taken at 30% polymer coating. The multiparticulates were cured and screened as described in Example 2.

Example 4: Preparation of delayed release (DR) Eudragit RS:RL (98:2) over-coated Rivastigmine multiparticulates.

Eudragit RS:RL (90:10)coated Rivastigmine multiparticulates (prepared according to Example 3) were coated with Eudragit RS: Eudragit RL (98:2) aqueous dispersion (prepared according to Example 2), using

triethyl citrate as plasticiser.

A polymer weight gain of 20% was over-coated to the Eudragit RS:RL (90:10) coated Rivastigmine multiparticulates, and an in process sample was taken at 10% polymer coating. The multiparticulates were cured and screened as described in Example 2.

Example 5: Preparation of delayed release (DR) Eudragit RS:L (75:25) coated Rivastigmine multiparticulates.

A Eudragit RS: Eudragit L (75:25) organic solution was prepared as follows: 4.650kg of isopropyl alcohol were stirred with 125g of triethyl citrate and 3.750kg of Eudragit RS12.5 for 5 minutes. 225g of talc (USP) were added and the mixture stirred for 15 minutes. 1.250kg of Eudragit L12.5 was added to the mixture and stirred for 30 minutes.

The resulting solution was sprayed onto instant release multiparticulates prepared according to Example 1, using a fluid bed apparatus as used in Example 1. Spray rate was 5-8.5g/min*kg, and the inlet temperature was 38-40°C. The instant release multiparticulates were maintained at 29-32°C. A polymer coating of 30% polymer weight gain was coated onto the instant release multiparticulates and an in process sample was taken at 20% polymer coating. The multiparticulates were cured and screened as described in Example 2.

Table 2 shows dissolution rates for the multiparticulates prepared in Examples 3, 4 and 5. Sample profiles are

illustrated in Figure 2.

Table 2

	Example 3		Example 4		Example 5	
	Eudragit RS: RL (90:10) TEC		Eudragit RS: RL (98:2) TEC overcoat		Eudragit RS: L (75:25) TEC	
Time	% released		% released		% released	
(hours)	30%	40%	10%	20%	20%	30%
1	0.9	8.3	NT	0	0	0.0
2	--	--		--	0.4	0.0
3	26.4	20.7		0.8	--	--
4	57.6	33.3		1.6	1.8	0.0
6	87.8	66.8		4.2	6.4	1.4
8	95.9	83.4		7.6	30.2	7.0
10	98.3	91.0		21.2	74.6	28.4
12	99.7	93.6		37.1	96.5	61.8

Example 6: Manufacture of instant release (IR) Rivastigmine minitablets.

Formulation details:

Material	%
Rivastigmine tartrate	13.7
Sodium starch glycolate	10
Microcrystalline cellulose	74.05
Colloidal silicon dioxide	1.5
Magnesium stearate	0.75

The instant release minitablets were produced by direct compression using the following method

1. Add a similar quantity of the microcrystalline cellulose to the drug and bag blend for 1 minute.
2. Add the colloidal silicon dioxide and bag blend for a further 1 minute
3. Screen the mix through a 600mm sieve
4. Add the remaining microcrystalline cellulose, the drug/microcrystalline cellulose/colloidal silicon dioxide mix and the sodium starch glycolate to a V cone blender and mix for 15 minutes at 18rpm.

Add the magnesium stearate and mix for a further 5 minutes at 18 rpm

Figure 3 shows a dissolution profile for instant release minitablets.

Example 7: Manufacture of sustained release (SR) Rivastigmine minitablets.

Formulation details:

Material	%
Rivastigmine tartrate	13.7
Hydroxypropyl cellulose	40
Microcrystalline cellulose	38.8
Colloidal silicon dioxide	1.5
Magnesium stearate	1

The Rivastigmine SR minitablets were produced by direct compression using the following method

1. Add a similar quantity of the microcrystalline cellulose to the drug and bag blend for 1 minute.

2. Add the colloidal silicon dioxide and bag blend for a further 1 minute

3. Screen the mix through a 600mm sieve

4. Add the remaining microcrystalline cellulose, the drug/microcrystalline cellulose/colloidal silicon dioxide mix, and the hydroxypropyl cellulose to a V cone blender and mix for 15 minutes at 18rpm.

5. Add the magnesium stearate and mix for a further 5 minutes at 18 rpm

Example 8: Coating of minitablets from Example 6 with the pH independent polymer Eudragit RS:RL (98:2).

A Eudragit RS: RL (98:2) aqueous dispersion was prepared as follows:

0.5g of simethicone emulsion USP, 12g of triethyl citrate and 36g of talc USP were added with mixing to 251.5g of purified water. The mixture was stirred for 15 minutes using a mixer at 1200rpm. This suspension was then added to 196g of Eudragit RS30D and 4g of Eudragit RL30D (ammonio methacrylate co-polymers in the form of aqueous dispersions from Röhm Pharma, Germany) and stirred for 20 minutes.

The resulting dispersion was sprayed onto minitablets as manufactured in step 1a, using a fluidised bed coater with Wurster column insert. The spray rate was 3.7-5.7g/min, the inlet temperature was 30-39°C and the bed temperature 28-32°C. A coating of 20% polymer weight gain was applied and the tablets dried within the fluidised bed coater for 15 minutes and then dried for 40 hours in an oven.

Figure 4 shows dissolution profiles for these minitablet formulations.

Example 9: Coating of minitablets from Example 6 with the pH dependent polymer Eudragit S 12.5.

A Eudragit S 12.5 organic dispersion was prepared as follows:

32g of dibutyl sebecate was added to 77g of purified water, this suspension was then added to 1.081kg of isopropyl alcohol and mixed for 5 minutes. 1.247kg of Eudragit S 12.5 was added into the solution and mixed for 5 minutes. Finally 63g of sterilised talc was added and the suspension mixed for 20 minutes.

The resulting dispersion was sprayed onto the sustained release minitablets from Example 6 using a fluidised bed coater with a Wurster column insert. The spray rate was 8.4-10.4g/min and the inlet temperature 38-47°C. The minitablets were maintained at approximately 33°C. A coating of 20% polymer weight gain was coated onto the minitablets with an in-process sample being taken at 15%

polymer weight gain, the minitablets were dried for 15 minutes before removal from the fluidised bed coater.

Dissolution profiles for these minitablet formulations are shown in Figure 5.

Example 10: Coencapsulation of multiparticulates with minitablets.

Sustained release Rivastigmine minitablets, and delayed release Rivastigmine multiparticulates, were formulated as detailed below and coencapsulated into hard gelatin capsules.

Minitablets:

Component	mg/capsule
Rivastigmine HTA	4.8
Methocel K100LV	14.0
Avicel PH101	15.3
Aerosil 200	0.5
Magnesium Stearate	0.4

Multiparticulates:

Component	mg/capsule
Rivastigmine HTA	4.8
HPMC 3cps *	1.6
Silicon dioxide	0.8
N.P Seeds	52.8
Eudragit RS	8.9
Eudragit L	3.0
Triethyl citrate	2.4
Talc	4.8

Table 3 shows dissolution profiles for the individual components. These profiles are illustrated in Figure 6.

Table 3

	Minitablets 40% Methocel K100LV	Multiparticulates 20% Eudragit RS:L (75:25) TEC
Time (hours)	% released	% released
0.5	42.1	--
1	72.7	0
2	83.3	0.4
3	--	--
4	93.0	1.8
6	92.8	6.4
8	--	30.2
10	--	74.6
12	--	96.5

Example 11: Coencapsulation of sustained release Rivastigmine multiparticulates and delayed release Rivastigmine multiparticulates.

Sustained release Eudragit RS:RL (98:2) coated Rivastigmine multiparticulates were coencapsulated with each of three different delayed release multiparticulates. Instant release multiparticulates were prepared as described in Example 1, and were then coated with Eudragit RS:L (75:25) at 10%, Eudragit RS:L (75:25) at 15%, and Eudragit RS:L (65:35) at 15%.

Compositions of the three different co-encapsulated formulations are set out below:

Batch	1	
Composition	mg/capsule	
Component	SR	DR
Rivastigmine (Base)	4.8(3.0)	4.8(3.0)
HPMC 3cps.	1.6	1.6
Silicon Dioxide	0.8	0.8
Non-Pareil Seeds	52.8	52.8
Eudragit RS (as solid)	4.7	6.8
Eudragit RL (as solid)	0.1	n/a
Eudragit L (as solid)	n/a	2.2
Triethyl Citrate	1.0	1.8
Talc	2.9	3.3
Simethicone Emulsion	0.1	n/a
Size 3 Gelatin Capsule	one	one

Batch	2	
Composition	mg/capsule	
Component	SR	DR
Rivastigmine (Base)	4.8(3.0)	4.8(3.0)
HPMC 3cps	1.6	1.6
Silicon Dioxide	0.8	0.8
Non-Pareil Seeds	52.8	52.8
Eudragit RS (as solid)	4.7	4.5
Eudragit RL (as solid)	0.1	n/a
Eudragit L (as solid)	n/a	1.5
Triethyl Citrate	1.0	1.2
Talc	2.9	2.2
Simethicone Emulsion	0.1	n/a
Size 3 Gelatin Capsule	one	one

Batch	3	
Composition	mg/capsule	
Component	SR	DR
Rivastigmine (Base)	4.8(3.0)	4.8(3.0)
HPMC 3cps	1.6	1.6
Silicon Dioxide	0.8	0.8
Non-Pareil Seeds	52.8	52.8
Eudragit RS (as solid)	4.7	5.9
Eudragit RL (as solid)	0.1	n/a
Eudragit L (as solid)	n/a	3.1
Triethyl Citrate	1.0	1.8
Talc	2.9	3.3
Simethicone Emulsion	0.1	n/a
Size 3 Gelatin Capsule	one	one

CLAIMS:

1. A dosage form containing pharmaceutically active agent in two or more different formulations having different respective release times for the pharmaceutically active agent under enteric conditions.

2. A dosage form according to claim 1 in which the different formulations contain the same pharmaceutically active agent.

3. A dosage form according to claim 1 or 2 in which one set formulation is an instant release formulation and another said formulation is a delayed release formulation.

4. A dosage form according to any one of the preceding claims in which one said formulation is a sustained release formulation and another said formulation is a delayed release formulation.

5. A dosage form according to claim 3 or claim 4 in which the delayed release formulation has the pharmaceutically active agent surrounding by a release-delaying coat of polymeric material.

6. A dosage form according to claim 5 in which the release-delaying coat comprises a blend of two polymers having different permeabilities.

7. A dosage form according to claim 6 in which a more soluble of the two polymers is an acrylate or acrylic acid polymer modified with ionic groups.

8. A dosage form according to claim 6 or claim 7 in which the more soluble of the two polymers has a pH-dependent permeability, being more soluble under alkaline conditions than under acidic conditions.

9. A dosage form according to any one of the preceding claims in which one or more of said different formulations is/are provided as a plurality of particulates, a plurality of the particulates of the respective formulation being contained in a unit dosage form.

10. A dosage form according to claim 9 which has a capsule containing said plural particulates.

11. A delayed release pharmaceutical dosage form comprising pharmaceutically active agent and a release modifying coating containing a blend of polymeric materials having different permeabilities, a more permeable of the polymeric materials having a pH-dependent permeability, being more permeable under alkaline conditions than under acidic conditions.

12. A delayed release dosage form according to claim 11 in which said more permeable polymeric material comprises an acrylate and/or acrylic acid polymer, modified with ionic groups such as quaternary ammonium groups.

13. A method comprising the preparation of a dosage form according to any one of claims 1 to 12.

14. A method of administering a delayed dose of pharmaceutically active agent, or plural temporally-

spaced doses of pharmaceutically active agent, comprising administering a single dosage form according to any one of claims 1 to 12.

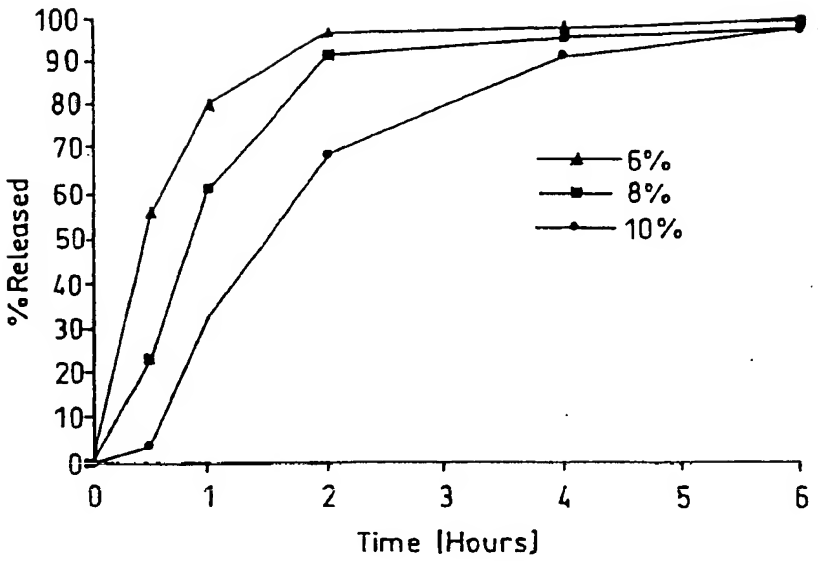

Fig.1.

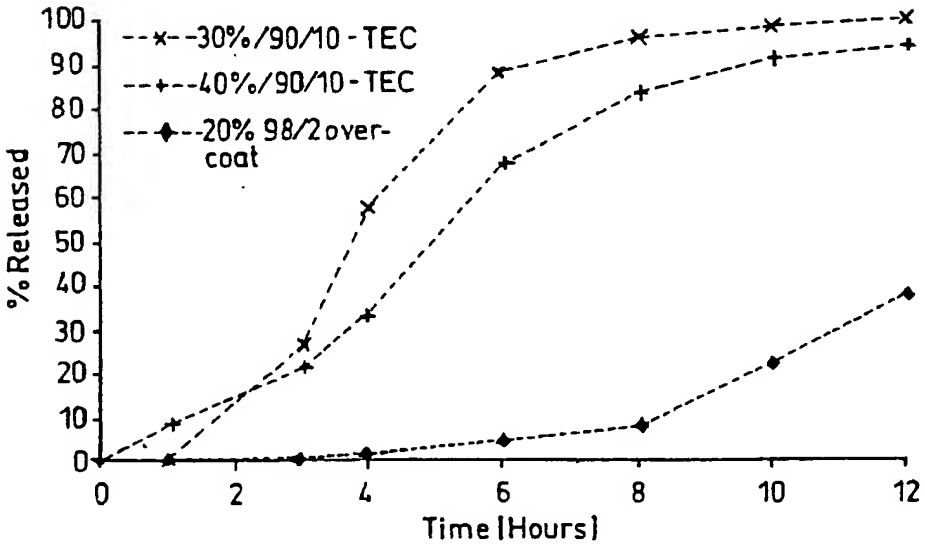

Fig.2.

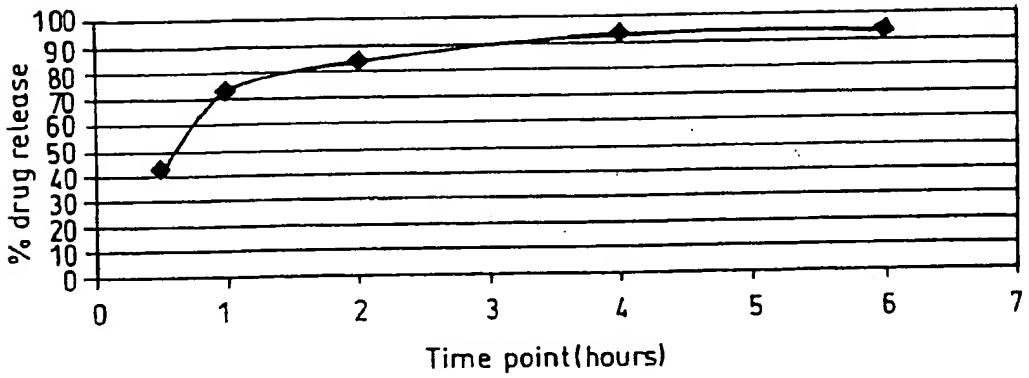

Fig.3.

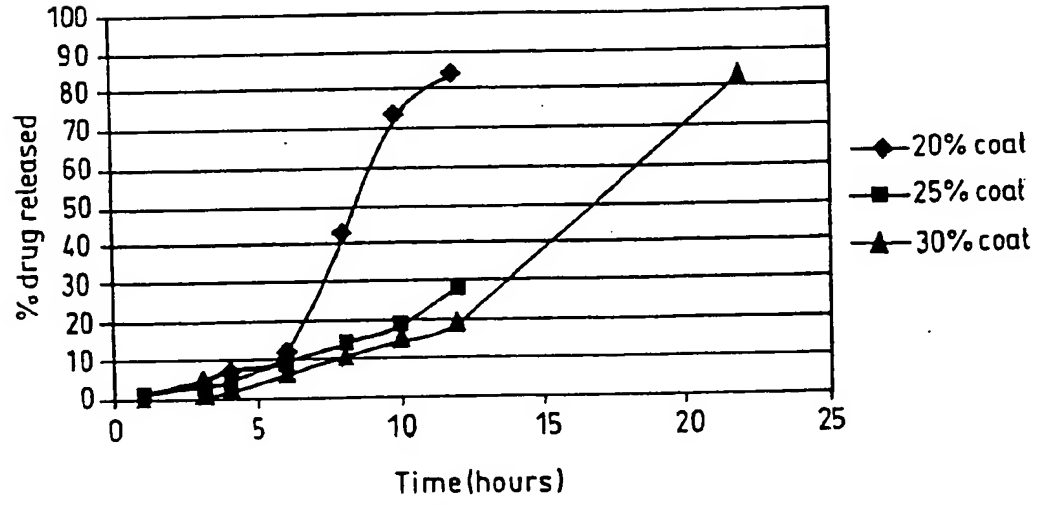

Fig.4.

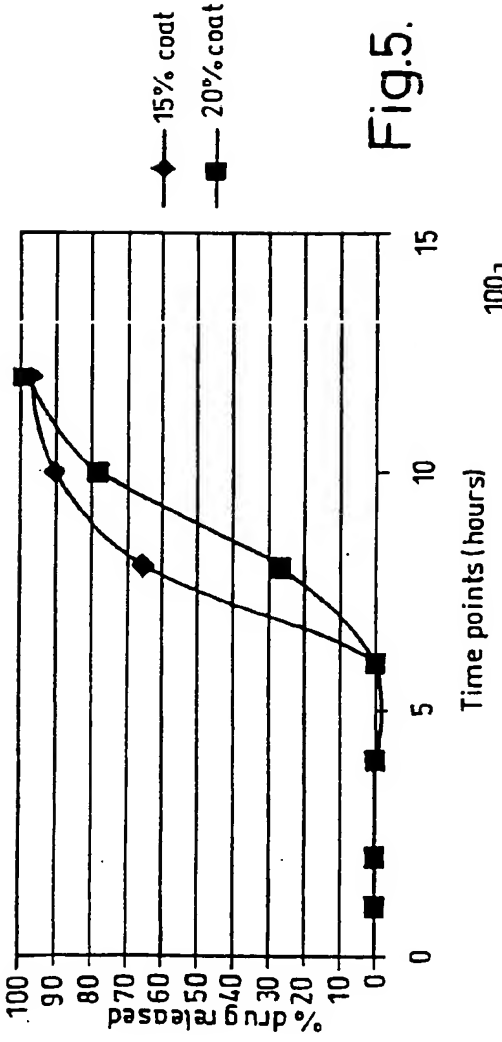

Fig.5.

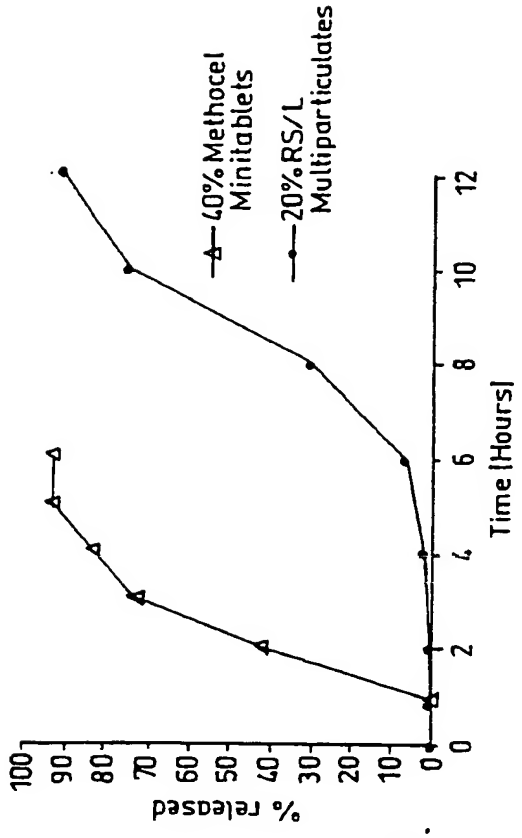

Fig.6.